Indian Journal of Fundamental and Applied Life Sciences ISSN: 2231– 6345 (Online)
An Open Access, Online International Journal Available at www.cibtech.org/sp.ed/jls/2015/01/jls.htm
2015 Vol.5 (S1), pp. 2887-2893/Rahmani et al.
Research Article

PROCALCITONIN: A NOVEL BLOODS MARKER IN CORONARY ARTERY DISEASE

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ABSTRACT

Introduction: Acute myocardial infarction (AMI) is the most common cause of death in the world. Conventional biomarkers of CK-MB, myoglobin and troponin I (TnI) don't have high confidence compared with the gold standard (angiography). This has led to improved decision-making process in this type of novel biomarkers of cardiac patients as Procalcitonin (PCT) used. ***Purpose:*** The aim of this study was to determine the levels of PCT in AMI and to investigate their possible correlation with the release of TnI, myoglobin and CK-MB. ***Materials and Methods:*** This study has been done on 135 patients suffering from coronary artery disease patients in three groups including: STEMI, N-STEMI and U/A tests. After obtaining blood serum samples from separate patients, biomarkers of PCT, myoglobin, CK-MB and TnI was measured. Quantitative values for each biomarker were measured by chemiluminescence method. Data analysis was performed using SPSS software, ANOVA and chi2 tests. ***Findings:*** PCT was elevated in all groups of patients. It was detected in serum approximately 2- 3 h after the onset of the symptoms of AMI. Variables of age, gender, family history of diabetes and a significant difference was found between the three groups. Generally, difference of PCT with above biomarkers at entry and four hours, except for patients with STEMI group was significant. ***Discussion & Conclusion:*** Considering the significant differences between PCT with mentioned biomarkers, it could be considered as a novel marker for diagnosis of AMI.

Keywords: *Procalcitonin, CK-MB, Troponin I, Acute Myocardial Infarction*

INTRODUCTION

Diagnosis of Acute coronary syndrome **(**ACS) is based on an assessment of risk factors, careful and rapid assessment of ECG, and measurement of cardiac enzymes. Cardiac troponins, creatinine kinase isoenzyme MB (CK-MB) and myoglobin, which are routinely used in the diagnosis of ACS, are not elevated in the initial hours, removing their value in an early diagnosis (Anthony *et al.,* 2008).

This has caused a kind of perplexity in diagnosis of acute heart stroke in some patients suffering from acute coronary syndrome. Therefore some patients are not diagnosed and are deprived of treatments. To improve decision- making process in patients suffering from acute coronary syndrome and myocardial infarction and to reduce the length of hospitalization, a lot of interest has appeared to use novel cardiac biomarkers such as PCT which is one of the fast methods of measurement if laboratory and bedside (Bektas *et al.,* 2011).

Various markers are suggested to diagnose patients suffering from acute cardiac problems. Nowadays despite these improvements because of normality of cardiac markers tests having obvious diagnosis value, many patients suffering from acute ischemic are ignored which won't have a favorable consequence for them. Therefore everyday novel diagnosis markers are suggested for these patients (Bektas *et al.,* 2011).

PCT (calcitonin precursor) is a new inflammatory marker with a protein structure which is helpful in early detection of inflammation causes in acute phases. Also worldwide studies are done about the relation between inflammatory diseases and PCT, among which some studies confirm the effect of this marker at the time of acute inflammation (Reinhart *et al.,* 2011; Tang *et al.,* 2009; Nobre *et al.,* 2008).

On the other hand in recent years PCT is proposed as special inflammation marker for bacterial infections. But the number of conducted studies about predicting amounts of this marker in patients suffering from non-infectious inflammation disease such as myocardial acute infarction is limited (Sinning *et al.*, 2011).

Practically limited studies are done in the field of heart diseases diagnosis and the relation between PCT serum levels with sickness intensity. In the mentioned studies the diagnostic, prognostic and treatment continuation of patients suffering from acute heart diseases such as MI, ACS and so on, are investigated which were not confirmed definitively.

Troponins also are new indicators which are useful not only in myocardial necrosis diagnosis but in classification of catching risk in different patients. Troponins are made from protein compounds of contractile units of muscles; and their role is to provide calcium-binding compounds in collection of troponin, tropomyosin, actin and myosin (Gilber *et al.*, 2003). Clinical studies have shown that myoglobin and TnI accompanied with isoenzyme CK-MB escalates after a heart stroke, and after a number of days comes back to the base (Strunz *et al.*, 2011). But a little escalation in the amount of TnI can be observed for 7 to 10 days. It seems that the primary increase of TnI is cytosolic and later increase is related to the release of TnI from myofibrils which are recovering in the heart. Also long term increase of troponin can be observed in some of the patients suffering from pectoral angina. Although most of studies indicate TnI increase in patients with heart disease, but the increase has also been observed in diseases other than heart problems. TnI increases in patients suffering from chronic obstructive pulmonary and is used in prognosis of hospitalized patients in intensive care units of chronic obstructive pulmonary acute attack (Jaffe *et al.*, 1996; Rosalki *et al.*, 2004). Of course at the present time CK-MB isoenzyme is still used as the best biochemical indicator in heart stroke diagnosis. The amount of CK-MB in myocardial constitutes 10 to 30 percent of total amount of creatine kinase. Because this isoenzyme is not considerably thick in tissues out of heart, it is considered a relatively specific cardiac index. It should also be mentioned that CK-MB sometimes increases in situations other than heart stroke (Apple, 1997; Baillard *et al.*, 2003; Martins *et al.*, 2009).

In the present study it is aimed to (i) measure changes of PCT serum levels (of first and fourth hours) in identifying different states of patients with ACS(ii) compare the diagnostic performance of PCT to that of serially measured myoglobin, CK-MB and cardiac TnI (cTnI) and to determine the relation between these changes (Sinning *et al.*, 2011; Bektas *et al.*, 2011; Ataoğlu *et al.*, 2010; Kelly *et al.*, 2010; Kafkas *et al.*, 2008).

MATERIALS AND METHODS

Methodology

This prospective study was conducted in 135 patients admitted with a chief complaint of chest pain to our emergency department. The patients were checked by cardiologist and because of suffering from acute coronary syndrome were sent to pathobiology laboratory for some medical tests. In this research patients are classified into three groups of STEMI, N-STEMI and U/A that their disease is diagnosed by emergency specialist based on clinical and paraclinical results. Definition of acute coronary syndrome Patients with ACS were classified into the following:

1. STEMI: defined as having ST-segment elevation ≥1 mm in two contiguous leads (or ≥2 mm in V1 to V3 leads) or new left bundle branch block together with chest pain for > 30 min and/or evidence of myonecrosis.
2. NSTEMI: defined as no ST-segment elevation on ECG despite chest pain for more than 30 min.
3. UA: defined as ischemic chest pain lasting more than 30 min with no evidence of myonecrosis or ST elevation (Sebnem *et al.*, 2011).

Patients with a malignant tumor, liver disorders and renal disorders, chronic rheumatoid arthritis, brain ischemia, acute mesenteric ischemia and pregnant women were excluded from the study.

When patients were satisfied and testimonial was signed and questionnaire was completed, 5 milliliter of blood sample was taken from fasting patients. Later their blood serum was separated to measure TnI,

Myoglobin, PCT and CK-MB and maintained in 70 degrees centigrade. Levels of conventional cardiac markers, namely CK-MB, TnI and myoglobin, were measured by in vitro quantitative electro chemiluminescence immunoassay (ECLIA), sandwich test-specific antibody system and myoglobin STAT (Short TurnAround Time) kits. TnI measurement was done by TnI kit made in Dia Sorin Company of Italy (REF 315.101) (Schneider *et al.*, 2007; Sebnem *et al.*, 2011).

PCT was measured by quantitative method of luminescence and using PCT LIAISON kit made in B.R.A.H.M.S company of Germany (REF 318.101) (Schneider *et al.*, 2007; Eisenhut, 2010).

CK-MB measurement was done by quantitative method of luminescence and using Liaison CK-MB kit (Eisenhut, 2010).

Statistical Analysis

Data analysis was done using SPSS software and ANOVA tests and Chi 2; and $P<0.05$ was determined as significance level. Continuous variables were calculated as mean ± SD and categorical variables were calculated as numbers and percentage of patients.

RESULTS AND DISCUSSION

Results

From among the 135 participants of the study 90 persons (66.67%) were men and 45 individuals (33.33%) were women. Also in U/A group 74.7% of patients were men (59 persons), in N-STEMI group 44.7% were men (17 persons), and in STEMI group 66.7% were men (12 persons); and sex variable among three groups of heart patients is significantly different (P Value=0.02). The mean age of patients was 50 ± 16. Also the mean age of patients in U/A group was 63± 8, in N-STEMI group was 69± 6 and in STEMI group was 62 ± 5 which shows that age variable among three groups of patients is significantly different (P Value= 0.000). Also 79 persons of patients were U/A, 38 persons were N-STEMI and 18 persons of them were of STEMI type.

Table 1: Frequency of Diabetes history, Smoking, Family History and High Blood Pressure in Patients whit Separated Groups

Group Disease	STEMI	N-STEMI	UA	Significance Level
Total Cholesterol	188.4	193.7	184.1	0.01
Triglycerides	159.2	141.2	160.8	NS
Diabetes	56	51	58	0.01
Smoking	42	41	27	0.01
Family History of CAD	38	26	15	0.02
Hypertension	47	54	56	0.01

Frequency of diabetes, smoking, Total Cholesterol, Triglycerides, family history of CAD and hypertension in total are given in table 1. In diabetes, smoking, Total Cholesterol and family history of CAD there is significant difference among three groups of patients.

Table 2: Arrival and Fourth Hour Amount of PCT, CK-MB, TnI, Myoglobin(ng/ml) in Patients

Group	Control	UA	N-STEMI	STEMI
PCT (Arrival)	0.05±0.01	0.65±0.05	1.95±0.62	1.65 ±0.53
PCT (fourth Hour)	0.05±0.01	1.01 ±0.92	4.81±1.45	4.61±1.04
CK-MB (Arrival)	3.03±1.3	3.46±0.38	10.22±1.6	13.82±2.07
CK-MB (fourth Hour)	3.03±1.34	4.45±0.56	36.02±3.29	91.67±8.51
TnI(Arrival)	0.2±0.04	0.71±0.03	8.05±2.56	6.84±2.04
TnI(fourth Hour)	0.2±0.04	1.19±0.04	9.38±2.09	8.12±3.81
Myoglobin(Arrival)	37.1±10.9	30.28±4.51	174.2±27.29	191.11±34.57
Myoglobin(fourth Hour)	37.1±10.9	35.72±6.54	239.74±41.27	316.09±53.22

The mean Cardiac TnI levels in arrival STEMI (6.84±2.04), NSTEMI (8.05±2.56), and UA patients (0.71±0.03) were significantly higher than healthy volunteers (0.2±0.04) (Table 2).The mean CK-MB levels in arrival STEMI (13.82±2.07), NSTEMI (10.22±1.6) were significantly higher than healthy volunteers (3.03±1.34) and UA patients (3.46±0.38) (Table2). The mean serum myoglobin levels in arrival STEMI (191.11±34.57), NSTEMI (174.2±27.29) were significantly higher than healthy volunteers (37.1±10.9) and UA patients (30.28±4.51) (Table2). The mean serum PCT levels in arrival STEMI (1.65 ± 0.53), NSTEMI (1.95±0.62), and UA patients (0.65±0.05) were significantly higher than healthy volunteers (0.05±0.01) (Table2). The mean CK-MB levels in fourth hour STEMI (91.67±8.51), NSTEMI (36.02±3.29), and UA patients (4.45±0.56) were significantly higher than healthy volunteers (3.03±1.34) (Table2). The mean Cardiac TnI levels in fourth hour STEMI (8.12±3.81), NSTEMI (9.38 ±2.09), and UA patients (1.19±0.04) were significantly higher than healthy volunteers (0.2±0.04) (Table 2). The mean serum myoglobin levels in fourth hour STEMI (316.09±53.22), NSTEMI (239.74±41.27) were significantly higher than healthy volunteers (37.1±10.9) and UA patients (35.72±6.54) (Table2). The mean serum PCT levels in fourth hour STEMI (4.61±1.04), NSTEMI (4.81±1.45), and UA patients (1.01±0.92) were significantly higher than healthy volunteers (0.05±0.01) (Table 2).

Table 3: Relation of Arrival PCT of Patients with Arrival and Fourth hour TnI, Myoglobin and CK-MB

Patients Group	P Value of PCT:		
	CK-MB	Troponin I	Myoglobin
U/A group(Arrival)	0.00	0.00	0.00
U/A group (Fourth hour)	0.00	0.00	0.00
N-STEMI group(Arrival)	0.00	0.00	0.00
N-STEMI group (Fourth hour)	0.00	0.00	0.00
STEMI group(Arrival)	0.172	0.03	0.201
STEMI group(Fourth hour)	0.693	0.07	0.801

There was a significant difference between arrival PCT in U/A group with STEMI and N-STEMI groups (P =0.00). This means that PCT amount in U/A group was less than STEMI and N-STEMI groups but this difference between two groups of STEMI and N-STEMI was not significant (Table 3). PCT amount of fourth hour in U/A group had significant difference with STEMI and N-STEMI groups (P=0.00). This means that PCT amount in U/A group was less than STEMI and N-STEMI groups. But this difference between STEMI and N-STEMI groups was not significant (Table 3). Amount of arrival TnI in U/A group was significantly different with STEMI and N-STEMI groups (P=0.00). But the difference between two groups of STEMI and N-STEMI was not significant (Table 3). Amount of fourth hour TnI in U/A group was significantly different with STEMI and N-STEMI groups (P=0.00), but the difference between two groups of STEMI and N-STEMI was not significant (Table 3). Amount of arrival PCT had significant relation with arrival TnI (P=0.00) and also with arrival CK-MB (P=0.00) and myoglobin (P=0.00). In each group the results were as following: the relation between patients of N-STEMI groups for arrival PCT with TnI, myoglobin and CK-MB was significant but this difference was not significant for patients of STEMI group (Table 3). In every heart disease the results were as following: among patients of U/A group and N-STEMI the fourth hour PCT relation with fourth hour TnI, myoglobin and CK-MB was significant. In STEMI group fourth hour PCT relation was significant with TnI but insignificant with CK-MB and myoglobin (Table 3).

Discussion

Nowadays biomarkers are used in early diagnosis of many diseases and by novel technologies the markers sensitivity to diagnose diseases gets more (Eisenhut, 2010; Sentürk *et al.*, 2007). In recent years PCT biomarker due to its low level of plasma in healthy people (0.5ng/ml) and its increase in less than three hours, is used in any inflammatory diseases (Sponholz *et al.*, 2006; Brunkhorst *et al.*, 1999; Picariello *et al.*, 2011; Moya *et al.*, 1975).

On the other hand despite CK-MB, Myoglobin and TnI diagnosis markers' high diagnosis value in ACS, false positive cases of these tests increases waste of cost and doing intermediary diagnostic measures. In fact the belief that CK-MB and TnI only release in myocardial cell's irreversible damage is being reviewed (Rosalki *et al.,* 2004; Apple, 1998, Baillard *et al.,* 2003; Martins *et al.,* 2009). In a study on marathon runners PCT level significantly increased.

PCT has also increased in patients suffering from sepsis, malignant blood pressure, pulmonary embolism and kidney failure. According to researchers' idea stress in heart cells increases cardiac myocytes' penetration and is different from irreversible damage arising from cell death (Moya, 1975; Assicot, 1993; Maruna, 2000; Müller, 2001; Dandona, 1994; Meisner, 1998; Abbasi *et al.,* 2010; Kruif, 2010).

To confirm the diagnosis efficiency of a heart test and compare it with other methods there is a need to confirm it with a golden standard method.

Diagnosis golden standard in ACS is angiography and the level of PCT marker's sensitivity and diagnosis in detecting ACS must be confirmed by this method.

Based on this in the conducted study results show a relation between increase or decrease of markers and its importance exists in this relation, and based on this results are collected and analyzed.

Variables of age, sex, diabetes, Total Cholesterol, Triglycerides and family history of CAD was significantly different among three groups of heart patients; and in variables of Triglycerides there wasn't a significance difference among the groups. According to the results obtained from research this case is noteworthy. Prestige bias or prevarication bias can be effective in the results of these variables.

There is significant difference between arrivals PCT of the three groups, but the difference between two groups of STEMI and N-STEMI was not significant. Also fourth hour PCT level in the three groups was significantly different, but the difference between two groups of STEMI and N-STEMI was not significant. There was a significant difference in three groups about amount of arrival TnI but the difference between two groups of STEMI and N-STEMI was not significant. Also the fourth hour TnI level was significantly different among three groups but the difference between two groups of STEMI and N-STEMI was not significant.

Generally arrival and fourth hour PCT was significantly different with arrival and fourth hour TnI, Myoglobin and CK-MB except among patients of group STEMI.

Conclusion

PCT is proposed as a diagnosis biomarker in acute inflammatory phase. Studies done about the use of this marker in ACS diagnosis which is an inflammatory process improvably indicate its usability; but some other studies emphasize its inefficiency in diagnosis and see it only as a predictor of heart patients' survival. In the present study the results show that there is significance relation between PCT level changes with TnI, Myglobin and CK-MB as a new marker in ACS diagnosis.

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